U.S. App. No. 10/510,355

Filed: April 28, 2005

Response to Office Action filed December 12, 2008

Listing of Claims:

The listing of claims will replace all prior versions, and listings, of claims in the application:

1-43. (cancelled)

44. (Previously Presented) An agent for inhibiting at least one of release, maturation and

replication of a member of the Flaviviridae family selected from Flavivirus or Pestivirus and

Hepacivirus-wherein the agent comprises, as an active component, at least one proteasome

inhibitor in a pharmaceutical preparation.

45. (Previously Presented) An agent as claimed in claim 44, wherein the agent is used for the

treatment and prophylaxis of HCV-induced hepatitides, flavivirus-induced fever, hemorrhages,

leukopenia, thrombocytopenia, diarrheal diseases encephalitides or pestivirus-induced diseases.

46. (Previously Presented) An agent as claimed in claim 45, wherein the proteasome inhibitor is

a substance which inhibits, regulates or otherwise affects the activities of the

ubiquitin/proteasome pathway; which specifically affects the enzymic activities of the complete

26S proteasome complex; and which specifically affects the enzymic activities of the free 20S,

catalytically active, proteasome complex, which is not assembled with regulatory subunits.

47. (Previously Presented) An agent as claimed in claim 45, wherein the proteasome inhibitor is

taken up by higher eukaryotic cells and, after having been taken up into a cell, interacts with the

catalytic subunits of the proteasome, and, in connection with this, blocks at least some of the

proteolytic activities of the proteasome within the 26S or the 20S proteasome complex.

4

U.S. App. No. 10/510,355

Filed: April 28, 2005

Response to Office Action filed December 12, 2008

48. (Previously Presented) An agent as claimed in claim 45, wherein in addition to proteasome

inhibitors, the pharmaceutical preparation also comprises at least one further agent which affects,

regulates or inhibits the cellular ubiquitin system, such as the activities of the ubiquitin-

conjugating enzymes and/or of the ubiquitin-hydrolyzing enzymes.

49. (Previously Presented) An agent as claimed in claim 45, wherein the proteasome inhibitor is

administered in various forms in vivo, i.e. orally, intravenously, intramuscularly, subcutaneously

or in encapsulated form, with or without cell specificity-carrying changes, which, due to using a

particular administration and/or dose regime, exhibit low cytotoxicity, which do not elicit any

side effects, or only elicit insignificant side effects, and which exhibit a relatively high metabolic

half life and a relatively low clearance rate in the body.

50. (Previously Presented) An agent as claimed in claim 45, wherein the proteasome inhibitor

- a) is isolated in natural form from microorganisms or other natural sources; or
- b) is formed from natural substances as a result of chemical modifications; or
- c) is prepared completely synthetically; or
- d) is synthesized *in vivo* using gene therapy methods.

51. (Previously Presented) An agent as claimed in claim 50, wherein the proteasome inhibitor

belongs to the following substance classes:

a) naturally occurring proteasome inhibitors:

peptide derivatives which contain epoxyketone structures C-terminally,

5

- β-lactone derivatives,
- aclacinomycin A (also termed aclarubicin),
- lactacystin and its chemically modified variants, such as the cell membranepenetrating variant "clastolactacystein β-lactone"
- b) synthetically prepared proteasome inhibitors:
- modified peptide aldehydes, such as N-carbobenzoxy-L-leucinyl-L-leucinyl-L-leucinyl-L-leucinal (also designated MG132 or zLLL), its boric acid derivative MG232; N-carbobenzoxy-Leu-Leu-Nva-H (designated MG115; N-acetyl-L-leucinyl-L-leucinyl-L-norleucinal (designated LLnL) and N-carbobenzoxy-Ile-Glu(OBut)-Ala-Leu-H (also designated PSI);
- c) peptides which carry an α,β -epoxy ketone structure C-terminally, and also vinylsulfones, such as carbobenzoxy-L-leucinyl-L-leucinyl-L-leucinevinylsulfone, or 4-hydroxy-5-iodo-3-nitrophenylacetyl-L-leucinyl-L-leucinyl-L-leucinylsulfone (NLVS)
- d) glyoxylic acid or boric acid radicals, such as pyrazyl-CONH(CHPhe)CONH(CHisobutyl)B(OH)₂) and also dipeptidyl boric acid derivatives, or
- e) pinacol esters, such as benzyloxycarbonyl(Cbz)-Leu-Leu-boroLeu pinacol ester.
- 52. (Previously Presented) An agent as claimed in claim 50 wherein the particularly suitable proteasome inhibitor is the epoxyketone epoxomic (epoxomycin, molecular formula: $C_{28}H_{86}N_4O_7$) and/or eponemic (eponemycin, molecular formula: $C_{20}H_{36}N_2O_5$).

- 53. (Previously Presented) An agent as claimed in claim 50 wherein the particularly suitable proteasome inhibitor is selected from the PS series
 - a) PS-519 as β -lactone, and also as lactacystin derivative the compound IR-[1S,4R,5S]]-1-(1-hydroxy-2-methylpropyl)-4-propyl-6-oxa-2-azabicyclo[3.2.0]heptane-3,7-dione molecular formula $C_{12}H_{19}NO_4$ and/or
 - b) PS-341 as peptidyl-boric acid derivative the compound N-pyrazinecarbonyl-L-phenylalanine-L-leucine-boric acid molecular formula C₁₉H₂₅BN₄O₄ and/or
 - c) PS-273 (morpholine-CONH-(CH-naphthyl)-CONH-(CH-isobutyl)-B(OH)2) and its enantiomer PS-293 and/or
 - d) compound PS-296 (8-quinolylsulfonyl-CONH-(CH-naphthyl)-CONH(-CH-isobutyl)-B(OH)₂) and/or
 - e) PS-303 (NH₂(CH-naphthyl)-CONH-(CH-isobutyl)-B(OH)₂) and/or
 - f) PS-321 as (morpholine-CONH-(CH-naphthyl)-CONH-(CH-phenylalanine)-B(OH)₂); and/or
 - g) PS-334 (CH₃-NH-(CH-naphthyl-CONH-(CH-isobutyl)-B(OH)₂) and/or
 - h) the compound PS-325 (2-quinol-CONH-(CH-homo-phenylalanine)-CONH-(CH-isobutyl)-B(OH)₂) and/or
 - i) PS-352 (phenylalanine-CH₂-CH₂-CONH-(CH-phenylalanine)-CONH-(CH-isobutyl)1-B(OH)₂) and/or

U.S. App. No. 10/510,355

Filed: April 28, 2005

Response to Office Action filed December 12, 2008

j) PS-383 (pyridyl-CONH-(CH*p*F-phenylalanine)-CONH-(CH-isobutyl)-B(OH)₂).

54. (Previously Presented) A method of inhibiting at least one of the entry/internalization process, the replication and the maturation and release of Flaviviridae with the agent of claim 44.

55-86. (withdrawn)